Allergic Reactions to Vaccines Seminar 4009 Orlando March 5, 2012

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Faculty Disclosure Information

- I have not had a significant financial interest or other relationship with the manufacturers of the products or providers of the services that will be discussed in my presentation.
- This presentation will not include discussion of pharmaceuticals or devices that have not been approved by the FDA, but will include some discussion of non-FDA approved skin test materials.

Objectives

- Appreciate the nature of IgE-mediated and non-IgE-mediated adverse reactions to various vaccines.
- Develop a diagnostic approach to the evaluation of adverse reaction to vaccines including skin testing where appropriate.
- Provide advice to patients and families regarding the future administration of vaccines after an adverse reaction to a previously administered vaccine.
- Safely administer influenza vaccine to egg-allergic recipients

Adverse Reactions to Vaccines Practice Parameter 2011 Update (in press)

Summary Statement 1. Mild local reactions and constitutional symptoms, such as fever, after vaccinations are common and do not contraindicate future doses. Rarely, delayed-type hypersensitivity to a vaccine constituent may cause an injection site nodule, but this is not a contraindication to subsequent vaccination.

Summary Statement 2. Anaphylactic reactions to vaccines are estimated to occur at a rate of approximately 1 per million doses. There are approximately 220 million doses of vaccines administered in the United States each year.

Summary Statement 3. All serious events occurring after vaccine administration should be reported to the Vaccine Adverse Event Reporting System, even if it is not certain that the vaccine was causal.

Summary Statement 4. Measuring levels of IgG antibody to the immunizing agent in a vaccine suspected of causing a serious adverse reaction to determine if they are at protective levels can help determine whether or not subsequent doses are required.

Table 1. Levels of antibody associated with protection from vaccine-preventable diseases

Vaccine	Protective level of IgG antibody ≥:
Diphtheria	0.1 IU/mL
Haemophilus influenzae b	0.15 μg/mL
Hepatitis A	10 mIU/mL
Hepatitis B Surface Antibody	10 mIU/mL
Measles (Rubeola)	120 PRN titer
Polio (Inactivated)	1:8 neutralizing antibody titer
Rabies	0.5 IU VNA/mL
Rubella	10 IU/mL
Tetanus	0.1 IU/mL
Yellow fever	0.7 IU/mL

Abbreviations: IU, international units; mIU, milli-international units; PRN, plaque reduction neutralization; VNA, virus-neutralizing antibodies

- Even if the recommended number of doses has already been received or protective antibody levels have already been achieved, evaluation of the reaction, including skin testing if indicated, should be undertaken

Summary Statement 5. All suspected anaphylactic reactions to vaccines should ideally be evaluated in an attempt to determine the culprit allergen.

- When a patient experiences an apparently IgE-mediated reaction after an immunization, often labeled “allergic” and advised against future doses
- This approach should be avoided because it may leave patients inadequately immunized if they unnecessarily avoid vaccines to which they are not allergic or if the vaccine could be administered safely despite their allergy.
- In addition, not knowing the constituent of a vaccine to which the patient is allergic may pose a risk with future vaccinations that contain the same ingredient.

Summary Statement 6. IgE-mediated reactions to vaccines are more often caused by vaccine components such as gelatin, rather than the immunizing agent itself.

Gelatin

- Gelatin is added to many vaccines as a stabilizer
- Gelatin in vaccines is bovine or porcine, which are extensively cross-reactive
- Responsible for many anaphylactic reactions to MMR, varicella, and Japanese encephalitis vaccines.
- Vaccine makers in Japan and Germany removed gelatin or changed to a less allergenic gelatin with a decrease in allergic reactions

- A history of allergy to the *ingestion* of gelatin should be sought before the giving a gelatin-containing vaccine; negative history may not exclude an allergic reaction to gelatin *injected* with the vaccine.

- Persons who react to gelatin on ingestion should be evaluated by an allergist prior to administration of gelatin-containing vaccines.
- If the history is consistent with an immediate-type allergic reaction to gelatin confirmed by skin tests or serum specific IgE, skin test with vaccines prior to administration.
  - If negative, give in usual manner but observe for 30 minutes afterward.
  - If positive, give vaccine in graded doses

Table 2. Gelatin Content of Vaccines 2011

Vaccine	Gelatin Content
Influenza (Fluzone, Sanofi Pasteur)	250 micrograms per 0.5 ml dose
Influenza (FluMist, MedImmune Vaccines, Gaithersburg, Maryland)	2000 micrograms per 0.2 ml dose
Measles, Mumps, Rubella (ATTENUVAX, MERUVAXII, MMRII, MUMPSVAX, Merck, Whitehouse Station, New Jersey)	14,500 micrograms per 0.5 ml dose
Measles, Mumps, Rubella, Varicella (ProQuad, Merck)	11,000 micrograms per 0.5 ml dose
Rabies (RabAvert, Novartis, Emeryville, California)	12,000 micrograms per 1.0 ml dose
Typhoid Vaccine Live Oral Ty21a (VIVOTIF, Berna, Coral Gables, Florida)	capsule
Varicella (VARIVAX, Merck)	12,500 micrograms per 0.5 ml dose
Yellow Fever (YF-VAX, Sanofi Pasteur)	7,500 micrograms per 0.5 ml dose
Zoster (ZOSTAVAX, Merck)	15,580 micrograms per 0.65 ml dose

Egg

- Measles and mumps vaccines and one type of rabies vaccine are grown in chick embryo fibroblast cultures and contain negligible or no egg protein
- Thus, MMR can be administered to egg allergic children without skin testing and without adverse reactions
- Egg protein is present in higher amounts in yellow fever and influenza vaccines and could in theory cause reactions in egg allergic patients.

Influenza vaccination of egg-allergic patients

- Patients who have IgE-mediated egg allergy have a theoretical risk of anaphylaxis if injected with influenza vaccines containing egg protein.
- Withholding influenza vaccine from egg-allergic recipients has very real risk, namely the morbidity and mortality associated with the disease.

Influenza vaccine contains measurable quantities of egg protein (ovalbumin); does this cause systemic reactions when injected into egg-allergic patients?

- 7 published studies involving >1600 egg-allergic subjects getting influenza vaccine without *any* serious reactions (no respiratory distress or hypotension), and with only a low rate of minor reactions (hives, mild wheezing).
- So, the answer appears to be no.

But what about patients with severe egg allergy?

- Most studies have specifically *included* patients with histories of severe anaphylaxis (n = 185) with egg ingestion and these patients also tolerate the vaccine.
- So, even these patients do not appear to be at risk of serious reaction.

Does skin testing with the vaccine help predict a reaction?

- In one study, the vaccine was withheld from patients with positive skin tests but…
- In the studies where skin testing was done, vaccinated skin test positive subjects had no reactions, or no greater rate of reactions, than skin test negative subjects
- The rate (low) of reactions (minor) is the same whether skin testing is included in the protocol or not.
- So, the answer appears to be no.

Does dividing the dose (10% and if no reaction after 30 minutes 90%) reduce the rate of reactions?

- In those studies that divide the dose, the vast majority of patients ultimately tolerate the 10+90%
- Studies with single dose also report no serious reactions
- So, the answer appears to be no.

Why are there no serious reactions being reported?

- In those studies reporting the ovalbumin level, vaccines used have contained as much as 0.7 mcg per 0.5 mL dose without serious reactions, so at least that much is tolerated.
- Such data on “safe” ovalbumin levels is based on analyzing content of vaccines used in various studies, not a dose-response study. Thus, it is not known what amount of ovalbumin per dose might be associated with a higher rate of reactions or more severe reactions.

Why are there no serious reactions being reported?

- 3/4 manufacturers of injectable trivalent influenza vaccine (TIV) report the maximum amount of ovalbumin in the package insert and the other will provide the information on request.
- The claimed amounts are all < 1 mcg per 0.5 mL dose.
- The measured amounts in independent laboratories are usually much lower than the claimed amounts.

Why are there no serious reactions being reported?

- So the answer is likely that there is just not enough ovalbumin in the vaccine to cause a reaction.

What about LAIV?

- Although the intranasally-administered live attenuated influenza vaccine (LAIV) contains a low amount of ovalbumin, all published studies to date have evaluated the injectable trivalent inactivated vaccine (TIV), and thus TIV rather than LAIV should be used for egg-allergic recipients.
- Also LAIV should not be used in children with asthma, which often coexists with egg allergy.

TABLE 2. Ovalbumin content of injectable trivalent Influenza vaccines (TIV) approved for the 2011-12 season

Brand name	Manufacturer	Approved ages	Ovalbumin content (mcg per 0.5 mL dose*)†
Afluria	CSL Biotherapies (Merck)	≥ 9 years	≤ 1
Fluarix	GlaxoSmithKline	≥ 3 years	≤ 0.05
FluLaval	ID Biomedical Corporation of Quebec (GlaxoSmithKline)	≥ 18 years	≤ 1
Fluvirin	Novartis	≥ 4 years	≤ 1
Fluzone	Sanofi Pasteur	≥ 6 months	~0.1
Fluzone High-Dose	Sanofi Pasteur	≥ 65 years	~0.1

*Dose 0.25 mL 6-35 months, 0.5 mL ≥ 3 years

† Information in package inserts except Fluzone and Fluzone High-Dose from Sanofi Pasteur by telephone (1-800-822-2463) or e-mail (MIS.Emails@sanofipasteur.com)

Conclusions

1. Egg allergy of any severity (including anaphylaxis) is not a contraindication to the administration of influenza vaccine, but rather a precaution. The risk of not vaccinating is greater than the risk of vaccinating.
2. Patients who report that they are egg-allergic should be referred to an allergist, where the current status of the patient's egg-allergy (often outgrown) can be assessed by history and skin or blood tests for IgE antibody to egg, but this should not delay their influenza vaccination.

Conclusions

3. Skin testing egg-allergic persons with influenza vaccine prior to administration is not recommended because of its low sensitivity and specificity in predicting serious reactions to vaccine administration.
4. Dividing the dose of vaccine is also not required because the majority of even severely egg-allergic patients can tolerate the full vaccine dose without severe reaction.
5. All influenza vaccines available in the US contain low amounts of ovalbumin.

Conclusions

6. Influenza vaccine should be administered to those who are egg-allergic in a setting where anaphylaxis can be recognized and immediately treated should it occur and patients should remain under observation for at least 30 minutes after vaccination.
7. Egg-allergic patients with a history of hives only after egg ingestion can receive influenza vaccine in a primary care provider's office provided the appropriate personnel and equipment are available, while those with a history of more severe reactions to egg ingestion should receive their vaccine in an allergist's office.

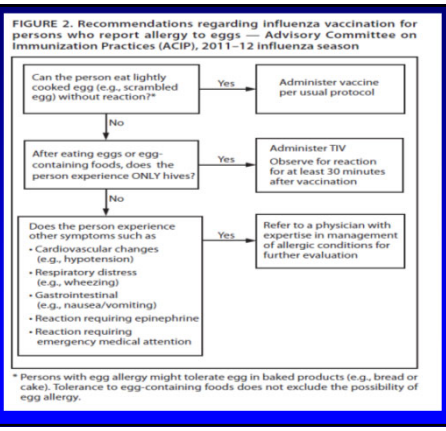


FIGURE 2. Recommendations regarding influenza vaccination for persons who report allergy to eggs — Advisory Committee on Immunization Practices (ACIP), 2011–12 influenza season

ACIP reference on influenza vaccine and egg allergy

- Prevention and Control of Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2011. MMWR Morb Mortal Wkly Rep 2011; 60:1128-32.

AAP reference on influenza vaccine and egg allergy

- Recommendations for prevention and control of influenza in children, 2011-2012. Pediatrics 2011; 128:813-25.

- A history of allergy after the ingestion of egg should be sought prior to the administration of yellow fever vaccine
- Persons with positive histories should be skin tested with yellow fever vaccine prior to administration
  - If negative, give in usual manner but observe for 30 minutes afterward.
  - If positive, give vaccine in graded doses

Yeast

- Hepatitis B vaccines are grown in *Saccharomyces cerevisiae* (baker's yeast or brewer's yeast) and contain residual yeast protein
- However, adverse reactions to these, if any, appear to be rare
- Human papillomavirus vaccine may also contain residual yeast protein

- Yeast allergy itself is very rare but, if a patient has a history of clinical reactivity to Baker's or Brewer's yeast and a positive skin test to *Saccharomyces cerevisiae*, skin test them with yeast-containing vaccines prior to administration.
  - If negative, give in usual manner but observe for 30 minutes afterward.
  - If positive, give vaccine in graded doses

Latex

- The "rubber" in vaccine vial stoppers or syringe plungers may be dry natural rubber (DNR) latex or synthetic rubber.
- Those made with DNR pose a theoretical risk to the latex allergic
- A review of > 160,000 VAERS reports found only 28 cases of possible immediate-type allergic reactions after receiving a DNR-containing vaccine, and these may have been due to other components

- Latex content of vaccine packaging is provided is updated at: http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/B/latex-table.pdf

- Patients with latex allergy can safely receive vaccines from vials with non-DNR stoppers.
- If the only available preparation has a latex stopper, the stopper should be removed and the vaccine drawn up directly from the vial without passing the needle through the stopper.
- If the only available vaccine contains latex in the packaging that cannot be avoided, such as in a prefilled syringe, the vaccine can still be administered but the patient should be observed for at least 30 minutes afterward.

Summary Statement 7. Patients who have had an apparent anaphylactic reaction after immunization should undergo immediate-type allergy skin testing to help confirm that the reaction was IgE-mediated and determine the responsible component of the vaccine.

- To determine whether a vaccine was responsible for an apparent allergic reaction, skin test with the vaccine
  - first by prick method (full-strength unless history truly life-threatening)
  - If negative, ID 1:100
- As with any (especially non-standardized) skin test reagent, false positive (irritant) and clinically irrelevant positive results may occur
- Likewise, false-negatives also possible

- If the suspect vaccine contains gelatin, egg, latex or yeast, skin test for these
- Egg and yeast extracts commercially available
- Gelatin (not FDA-approved): dissolve 1 teaspoon (5 g) of any sugared gelatin powder (e.g., Jell-O) in 5 mL of NS to create a prick skin test solution
- Latex (not FDA-approved): soak 2 fingers of latex glove or a toy balloon in 5 mL of NS to create a prick skin test solution
- In vitro assays for specific IgE antibody commercially available for gelatin, egg, latex and yeast

Summary Statement 8. If the intradermal skin test result is negative, the chance that the patient has IgE antibody to any vaccine constituent is negligible, and the vaccine can be administered in the usual manner. It is prudent nonetheless, in a patient with a history suggestive of an anaphylactic reaction, to administer the vaccine under observation with epinephrine and other treatment available.

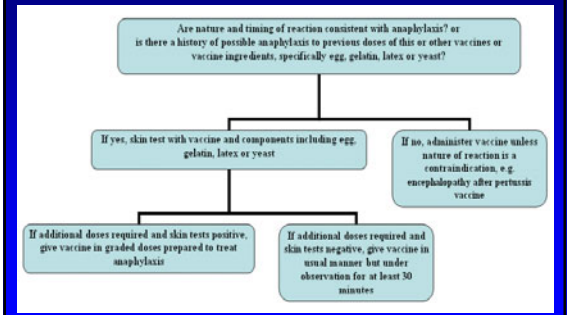
- No formal studies to evaluate the positive and negative predictive values for vaccine skin tests
- Dilutions of vaccines of 1:100 have been demonstrated to be nonirritating for intradermal testing
- No reports of patients with negative intradermal skin test reacting to subsequent administration of vaccine

Summary Statement 9. In patients with histories and skin test results consistent with an IgE-mediated reaction to a vaccine, who require additional doses of the suspect vaccine or other vaccines with common ingredients, consideration can be given to administering the vaccine in graded doses under observation.

- If vaccine or vaccine component skin test results are positive, the vaccine may still be administered, if necessary, in graded doses

Administration of Vaccines in Graded Doses
For a vaccine for which the full normal-dose volume is 0.5 mL, give the following doses at 15-minute intervals as tolerated
0.05 mL, 1:10 dilution
0.05 mL, full strength
0.1 mL, full strength
0.15 mL, full strength
0.2 mL, full strength

Suggested approach to suspected adverse reactions to a vaccine



Summary Statement 10. Some more serious, and less common, reactions to vaccines require evaluation, but only a few are absolute contraindications to future doses.

Guillain-Barre´ syndrome

- "Swine flu" vaccine administered in 1976 associated with increased risk GBS (1 additional case per 100,000 over background rate of 1 to 2 cases per 100,000)
- Subsequent years influenza vaccines have shown no consistent increased risk (If any, 1 per million)
- Specific attention was paid to the potential for GBS after the 2009 pandemic influenza A (H1N1) vaccine campaign and no increased rate was found.

- GBS continues to be reported in temporal association with influenza infection itself
- Previous GBS has risk of a recurrence
- Persons who developed GBS within 6 weeks of influenza vaccination should avoid subsequent immunization
- However, individuals with a history of GBS unrelated to influenza infection or vaccination who would benefit from immunization can be vaccinated

MMR/MMRV

- For reasons that are not clear, when MMR given in a combination vaccine with varicella, i.e. MMRV, twofold higher risk of febrile seizures than if the MMR and varicella vaccines are given by separate injections at the same visit (one additional febrile seizure per 2500 children vaccinated)
- This increased risk exists only for the first dose of the vaccines
- For this reason, administer the MMR and varicella vaccines by separate injections at the same visit for the first dose, and combined as MMRV for the second dose

Tetanus toxoid sequelae

- Due to increasing rates of pertussis in adolescents and adults, Tdap as a replacement dose for Td is now recommended
- The recommended interval between doses of Td had been 10 years, with shorter intervals thought to be associated with increased rates of Arthus reactions.

Tetanus toxoid sequelae

- However, in a recent study, rates of injection site reactions to Tdap were no different in those vaccinated less than 2 years than in those vaccinated more than 2 years after previous Td.
- Another study found no higher rates of injection site reactions whether a Tdap-containing vaccine was administered one month after a Td-containing vaccine or placebo.
- Thus, now recommended that Tdap be given to all adolescents and adults (including those 65 years of age and older) regardless of interval since the last Td.

Yellow Fever sequelae

- YF vaccine associated with a rare, but very severe illness in adults, yellow fever vaccine-associated viscerotropic disease (YEL-AVD), resulting in fatalities from multi-system disease strikingly similar to yellow fever itself
- Has occurred in patients who are not known to be immunocompromised, but history of a thymus disorder and age >60 years risk factors
- Cause unknown
- Vaccine should not be given to patients unless they are at risk of acquiring yellow fever, typically by traveling to an area where the disease is endemic.

Summary Statement 11. Pregnant women should not be vaccinated with live vaccines. However, pregnant women should be given inactivated influenza vaccine, as well as tetanus and hepatitis B vaccine if otherwise indicated.

Summary Statement 12. In general, live vaccines should not be given to persons who are immune compromised because of a risk of generalized infection with the immunizing agent.

Live vs. Killed Vaccines

Live vaccines	Killed vaccines
Bacille Calmette-Guerin (BCG)	Diphtheria, tetanus and acellular pertussis (DTaP, Tdap)
Influenza (intranasal)	Diphtheria-tetanus (DT, Td)
Measles-mumps-rubella (MMR)	Hepatitis A
Oral poliovirus (OPV)	Hepatitis B
Rotavirus	Hib conjugates
Typhoid (oral)	Human papillomavirus (HPV)
Vaccinia (smallpox)	Inactivated poliovirus (IPV)
Varicella	Influenza (injectable)
Yellow fever	Japanese encephalitis
Zoster	Meningococcal
	Meningococcal conjugate
	Pneumococcal
	Pneumococcal conjugate
	Rabies
	Typhoid (injectable)

Summary Statement 13. Specific vaccines or vaccination in general have been purported to have long-term consequences including atopy, autism and multiple sclerosis. Epidemiologic studies have not supported such associations.

Summary

- Patients with suspected allergy to vaccines or vaccine components should be evaluated by an allergist
- Most patients with suspected allergy to vaccines can receive vaccination safely